REMARKS

Claims 20, 37 and 39, the independent claims herein have been amended to require that the promoter be the promoter of an endogenous gene. Support for this amendment is found, for example, on page 7 of the specification at line 5, on page 20 at line 22, and throughout the specification. In addition, the nature of the fluorophore is clarified in these independent claims and is supported on page 9, beginning at line 12.

As the claims are now limited to detection of expression under control of an endogenous promoter, claims 24, 27 and 30-34 are canceled as inconsistent, and claim 38 is canceled as redundant. Claim 25 has also been canceled to expedite prosecution. No new matter is added and entry of the amendment is respectfully requested.

The invention takes advantage of the ability whole body external fluorescent optical imaging to provide a non-invasive way to look at gene expression throughout the body at various locations. This method of imaging is adapted to the types of fluorophores described herein and is defined on page 8 at lines 9-16. Because the expression at various locations can be measured simultaneously, a holistic picture of gene expression can be obtained. The methods of the present invention are new to the art.

The Rejections

Claims 20-23, 25-9 and 37-38 were rejected as assertedly anticipated by Contag, *et al.* (U.S. 5,650,135). There is no rejection over the art of claims 39-40, which remain in the case.

In order for anticipation to be found, all of the claimed elements must be found in a single document and ordered in the manner required by the claims. This does not describe the disclosure of Contag. The portions of Contag referred to by the Office at column 3, lines 59-61 refer to monitoring the effects of therapeutic substance on the levels of an entity, such as a light emitting bacterium. Claims formerly pending herein related to promoters associated with infectious

agents have been canceled. There is no mention at the cited location of assessing expression of an endogenous promoter. It is true that lines 29-32 mention fluorescent proteins. However, it is apparent from reading the entire disclosure that fluorescent proteins were never used by Contag; rather, the work described by Contag utilizes a luciferase system which requires cofactors and substrates, a system explicitly excluded from the present claims.

The detection methods described by Contag do not include the required whole body external fluorescent optical imaging. The detection method described by Contag involves imaging photon emission from the light generating molecules – *i.e.*, luciferase - with a photodetector device. (See column 5, lines 14-16). A further description of the detection method of Contag is found at column 15, beginning at line 15. As is evident from the description that follows and extends to column 17, line 14, the detection method described by Contag involves photon counting, not fluorescent optical imaging. The remaining cited sections of Contag also fail to disclose measuring the expression only of an endogenous gene and fail to disclose whole body external fluorescent optical imaging.

Accordingly, two essential elements of the claims – *i.e.*, the use of a promoter from an endogenous gene and the use of whole body external fluorescent imaging are not described in the cited document. Since each element of the claim is not present, the rejection for anticipation may properly be withdrawn. Again, it is pointed out that there is no rejection over the art of claims 39-40.

Claims 20-34 were rejected as failing to comply with the written description requirement. It is appreciated that this rejection is not applied to claims 37-40. As to claims 20-23, 26 and 28-29, which remain in the case, applicants respectfully suggest that this rejection is inappropriate for the following reasons:

The apparent basis for this rejection is that there are no specific promoters listed that are known to be associated with disease states. The reason for this is two-fold. First, a large number of promoters associated with disease states is known in the art and what is known in the art need not be

repeated in the specification. For example, promoters of various onco genes are known to be associated with cancer. Second, and more germane, the invention does not lie in identifying promoters associated with disease. The invention assumes that such promoters are already known. The invention is directed to a method to assess the expression of the genes associated with these promoters. It has nothing to do with the initial identification of the promoter *per se*.

As to the unpredictability of the results of the screening test of claim 20, it should be pointed out that no screening test is completely predictable of anything. Clearly, if treatment or protocol is found to lower the expression level of a gene that is associated with a disease, the probability of the treatment or protocol being successful in treating the disease is considerably higher than that for a treatment or protocol that fails the screen. That is all screening tests are designed to do.

This, thus, appears to be a rejection for lack utility rather than lack of written description. Either rejection is inappropriate in the context of the present claims which are directed to a screening test. Complete predictability as to the effects of successful treatments or protocols when applied to the clinic is neither expected nor required to meet the statutory requirements.

Only claims 39 and 40 were rejected under 35 U.S.C. 112, paragraph 1, as failing to comply with the enablement requirement. It is noted with appreciation that claims 20-23, 26, 28-29 and 37 are free of this rejection.

There appear to be two facets of this rejection. First, the Office complains that there is no working example of causing a mutation and detecting an altered gene level. Of course, it is blackletter law that no exemplification is required if the manner of carrying out the invention is taught. And it is indeed taught by the application. Methods for producing transgenic animals that contain expression systems with a selected promoter and a reporter protein are well-known and are outlined on page 17 of the application, beginning at line 5 and continuing into page 21, line 21. As noted, techniques for inserting such expression systems are well-known.

The second basis for this rejection is apparently that evaluating the level of expression may not be fool-proof because "the change in intensity of the fluorophore may be the result of interaction with other gene products." This may be a possibility, but is clearly a rare event as fluorescent proteins of the type described herein have been used as reporter genes to measure levels of expression for many years. There are no known cases of such fluorescent proteins interacting with "other gene products" in any context. The Office has adduced no support for this concept.

Applicants believe that the two concerns raised by the Office have been addressed and withdrawal of the rejection of claims 39-40 for lack of enablement is respectfully requested.

Claim 24 and certain dependent claims were rejected as indefinite based on the word "derived". This basis for rejection is mooted by cancellation of claim 24.

Summary

Claims 20-23, 26, 28-29, 37 and 39-40 remain in the case. The anticipation rejection of claims 20-23, 26, 28-29 and 37 may be withdrawn as these claims require the promoter to be that of an endogenous gene and the detection method be by whole-body external fluorescent optical imaging. Neither of these limitations is disclosed in the cited Contag document. Claims 39-40 are already free of this rejection.

The written description rejection of claims 20-23, 26 and 28-29 is believed in error as it assumes that the invention is directed to identifying promoters associated with diseases. This is not the case. The invention assumes (and it is indeed true) that such promoters are already known and others will continue to be discovered. The invention assumes this knowledge and describes what to do with it. Under these circumstances, there is no need to list this known subject matter in the application. Claims 37 and 39-40 were not part of this rejection.

The rejection of claims 39-40 for asserted lack of enablement is obviated by noting that means to obtain animals that express reporter proteins under control of a chosen promoter are well-known in the art. Means for causing mutations are also well-known in the art. The speculation

that alteration in fluorescence level may be due to something other than levels of expression is not supported by documentation. Accordingly, this basis for rejection may be withdrawn.

In view of the foregoing, it is believed that claims 20-23, 26, 28-29, 37 and 39-40 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **312762002710**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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